**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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*Ex parte* BRENT R. STOCKWELL, ALEXIS BORISY, and MICHAEL A. FOLEY

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Appeal 2007-1158
Application 09/611,835
Technology Center 1600



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ON BRIEF

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Before ADAMS, MILLS, and LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

## DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 89-156. We have jurisdiction under 35 U.S.C. § 6(b). We reverse, but set forth a new ground of rejection over all pending claims.

## STATEMENT OF CASE

The claimed invention relates to a method of screening combinations of chemical compounds for an effect on a biological property of cells. Appellants assert to

> have invented a . . . new method for . . . systematically performing high throughput screens of combinations of compounds . . . to discover combinations that interact synergistically in biological systems. The methods of the invention can identify effective therapeutic combinations of compounds that exhibit previously unknown therapeutic effects even where each compound in the combination may have previously have had no recognized biological effect, and even where the compounds and the combination would not, a priori, have been obvious candidates to use in combination.

(Specification 4.) This is achieved by "screening two-entity or higher order combinations for biological activity." (Specification 4-7.)

Claims 89-156 stand rejected under 35 U.S.C. § 103(a) as obvious over Stylli (U.S. Pat. 5,985,214, issued Nov. 16, 1999). (Br. 1.) There are five independent claims, each of which involve the same method steps (Br. 2-3). For the purpose of deciding the appealed rejection, we focus on claim 89. Claim 89 reads as follows:

> A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of
>
> (a) providing at least forty-nine unique combinations of at least seven different compounds,
>
> (b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,
>
> (c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,
>
> (d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal, and

> (e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells.

## ISSUE ON APPEAL

We frame the issue in this appeal as follows:

Whether Stylli would have reasonably suggested to the person of ordinary skill in the art at the time the invention was made screening "unique combinations" of different compounds in a method of "discovering . . . combinations of compounds having the ability to affect a biological property of living cells"?

## CLAIM INTERPRETATION

Claim 89 is directed to a method of screening combinations of compounds which affect a biological property of living cells. The method comprises six steps, a) through e), which involve "providing" unique combinations of drugs, "contacting" cells with the drug combinations, and "measuring" their effect on the properties of the cells. The purpose of the method is to discover a combination which has a greater effect on the cells than the effect of any individual compound which comprises it.

Step (a) requires "providing at least forty-nine unique combinations of at least seven different compounds." Words of a claim "are generally given

their ordinary and customary meaning." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576 (Fed. Cir. 1996). Giving "unique" its ordinary and customary meaning,[1] we interpret the term in the context of the whole phrase to indicate that each of the forty-nine "combinations" is different from each other. As required by the preamble of the claim ("a two or higher order combination of compounds"), each unique combination has at least two different compounds. In other words, the combinations are selected from seven different compounds and must contain at least two different compounds.

Claims "must be read in view of the specification, of which they are a part." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315, 75 USPQ2d 1321, 1327 (Fed. Cir. 2005). Our interpretation is consistent with the specification in which examples are provided of pair-wise combinations of seven different compounds, where each pair is different ("unique") from the other (Specification 34: 24-26).

The different drug combinations are contacted with test cells (step (b)) and their effect on the cells is measured or detected (step (c)), facilitating the identification of a combination which effects a biological property of the cells (step (d)).

In step (e), each compound in the combination "identified in step (d)" is tested for activity on the cells "at any time during said method." Because step (e) requires that (d) first be performed, we interpret "at any time during said method" to mean at any time after step (d) has been performed.

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[1] "Unique . . . 1. existing as the only one or as the sole example." *Random House Dictionary* 1436 (1982).

The combination in step (d) is identified as a "desired" combination "if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells." The total effect of the drug combination must be greater than any individual drug effect.

## THE CITED PRIOR ART

The only cited prior art is Stylli. The Examiner summarizes its disclosure as follows:

> Stylli et al. teaches an automated method and system for identifying chemicals having useful activity such as biological activities of chemicals and collecting information[] resulting from such a process (col. 6, lines 1-24). The method comprise[s] . . . testing a therapeutic chemical for modulating activity of a target such as cell surface proteins in a cell based assay (col. 38, lines 46-67; col. 39, lines 1-9; col. 43, lines 6-9). The method comprises dispensing the reagents (compounds) into the addressable sample wells, which contains a predetermined volume of the sample (test cells) (col. 6, lines 25-40; col. 8, lines 14-18). The method can individually screen at least 25,000 selected and discrete chemicals or chemical libraries wherein the chemicals are structurally related base on activity relationships (i.e. a combination of compounds) (col. 37, lines 44-51). Various method[s] of detection of the compound interaction with the target [are disclosed which] includes fluorescent measurement such as FRET (fluorescence resonance energy transfer) (col. 27, lines 29-35; col. 28, lines 15-17; col. 39, lines 1-67 thru col. 42, lines 1-23).

(Answer 3.)

## DISCUSSION

A prima facie case of obviousness requires evidence that the prior art disclosed or suggested all of the elements of the claimed invention, and that those skilled in the art would have been motivated to combine those elements with a reasonable expectation of success. *See In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970); *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991).

In this case, the Examiner asserts that Stylli teaches steps (b) through (e) of the claimed method (*see* Answer 3). The Examiner contends that step (a) of providing "forty-nine unique combinations of at least seven different compounds" is not expressly disclosed by Stylli (Answer 3), but would have been obvious to the person of ordinary skill in the art.

> One of ordinary skill in the art would have been motivated to include testing of forty-nine unique combinations of seven different compounds in the method of Stylli et al. because the number of combinations of compounds to be tested for the affect of biological property would be a choice of experimental design and is considered within the purview of the cited prior art.

(Answer 4.)

As evidence of obviousness, the Examiner points to disclosure in Stylli which the Examiner contends suggests "screening combinations of compounds," including combinations which include known therapeutic agents (Answer 5).

After reviewing Stylli in its entirety, we find that its disclosure would not have reasonably suggested to the person of ordinary skill in the art at the time the invention was made the claimed step (a) of "providing at least forty-

nine unique combinations of at least seven different compounds," where each combination has at least two different compounds. We do not agree with the Examiner that the disclosure at column 44, lines 20-23,[2] describes drug combinations that comprise known therapeutic agents for drug screening (Answer 5). As pointed out by Appellants, this disclosure is from the section of the patent titled "Pharmaceutical Compositions," beginning at column 43, line 45, which describes "pharmaceutical compositions prepared for storage and subsequent administration." (Col. 43, ll. 46-48.) Following the sentence cited by the Examiner at column 44, lines 20-23, there is a description of routes and dosages for administration of the pharmaceutical compositions. In our view, the skilled person reading this section would have understood the disclosure of "therapeutic agents" to be a reference to therapeutic use, not screening in Stylli's automated method.

At column 37, lines 51-52, Stylli states that its "system can also be used to create pools of chemicals."[3] This is a disclosure of "combinations" of compounds. However, we do not find this disclosure sufficiently specific or detailed to alone suggest providing pools of "unique" combinations as we have interpreted the claim. The Examiner offers no explanation on how this

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[2] "In practicing the methods of the invention, the products or compositions can be used alone or in combination with one another, or in combination with other therapeutic or diagnostic agents."

[3] Although the Examiner cited col. 37, l. to col. 38, l. 67, which contains the disclosure of "pools of chemicals," Appellants ignored this disclosure, stating that "the Examiner has inexplicably relied on a single sentence in Stylli" at col. 44, ll. 20-23 (Reply Br. 3).

statement would have led the skilled worker to use different "pools" as required by claim 89. The preponderance of the evidence does not support the Examiner's position. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("[P]atentability is determined on the totality of the record, by a preponderance of the evidence.").

Because the Examiner has failed to establish prima facie obviousness of the claimed subject matter, we reverse the rejection of claims 89-156.

## NEW GROUNDS OF REJECTION

Although Stylli alone is insufficient to sustain the rejection under § 103 because it fails to suggest screening "unique" combinations of compounds, we find that this missing element is described in the prior art. For this reason, we set forth the following new grounds of rejection pursuant to 37 C.F.R. § 41.50(b).

*Rejection of claims 89-99, 102-106, 108, 110, 112-124, 126, 129, 131, 133-140, 142, 145, 147, 149, 150, 152, and 154-156*

Claims 89-99, 102-106, 108, 110, 112-124, 126, 129, 131, 133-140, 142, 145, 147, 149, 150, 152, and 154-156 are rejected under 35 U.S.C. § 103(a) as obvious over Stylli in view of West (U.S. Pat. 6,368,789 B1, issued Apr. 9, 2002; filed Jun. 5, 1995), Burgin (U.S. Pat. 6,280,936 B1, issued Aug. 28, 2001; filed Jun. 9, 1998), and Chiang (U.S. Pat. 6,120,665, issued Sept. 19, 2000; filed Feb. 18, 1998).

As discussed *supra* at pp. 5-6, Stylli describes screening different chemical compounds for their effect on biological properties of living cells,

which meets the limitations of steps (a) through (d) of independent claims 89, 114, 135, 149, and 154, and dependent claim 156. However, Stylli does not teach screening "unique combinations" of different compounds as required by these claims. This element, however, was known in the art prior to the instant application filing date as evidenced by West, Burgin, and Chiang.

West describes methods of screening agents for their ability to inhibit telomerase activity in cells (col. 11, ll. 9-40). For screening large numbers of telomerase inhibitors, West teaches that different pools of inhibitors can be contacted with living cells (col. 11, ll. 41-43). As an illustration, West states:

> Thus, if a panel of 1,000 inhibitors is to be screened, all 1,000 inhibitors can potentially be placed into microtiter wells. If such an inhibitor is discovered, then the pool of 1,000 can be subdivided into 10 pools of 100 and the process repeated until an individual inhibitor is identified.

(Col. 11, ll. 43-48.)

Burgin describes methods for screening libraries of catalytic nucleic acid molecules for activity (col. 3, ll. 38-40; col. 5, l. 33 to col. 6, l. 34). "The method . . . involves systematic screening of a library or pool of ribozymes [catalytic nucleic acid] with various substitutions at one or more positions and selecting for ribozymes with desired function or characteristic or attribute." (Col. 3, ll. 39-44.) In preferred embodiments, Burgin describes the synthesis of different pools of ribozymes, where each pool differs in the position of a fixed nucleotide or the nucleotide identity at the fixed position (e.g., either A, T, G, or C at position $F_2$) within the ribozyme sequence (col. 5, ll. 39-66). "In the example illustrated in, FIG. 6, three

positions (designated positions 1, 2 and 3) are varied, so three different Classes of ribozyme pool are synthesized." (Col. 5, ll. 48-51.)

Finally, in discussing the use of combinatorial chemistry to identify new drugs, Chiang describes approaches in which different pools of chemicals are screened for pharmacological activity (col. 2, ll. 1-11).

"When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness." *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002). A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. "[T]he teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kahn*, 441 F.3d 977, 987-988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). In this case, each of West, Burgin, and Chiang establish that a well known approach to drug screening was to create pools of "unique combinations" of chemical compounds to systemically and efficiently identify the most active and promising compounds for further evaluation. Accordingly, we find that the nature of the problem of drug screening as a whole would have suggested utilizing unique combinations of chemicals for the reasons taught in the West, Burgin, and Chiang patents.

These patents also teach that the number of compounds present in each pool, as well as the number of pools, depends on the particular design of the screening method. For instance, in Burgin, the number of pools was based on the number of different nucleotides or analogs chosen to substitute at a given fixed position (col. 5, ll. 59-65). In West, the pool and combination number was based on the number of compounds to be screened and how many compounds were to be included in each pool (col. 11, ll. 43-48). Based on this evidence, we conclude that the choice of the specific number of pools and chemical compound members in each pool is the type of selection that is routinely made in high throughput drug screening by the person of ordinary skill in the art. Accordingly, although the references do not describe the specific unique numbers of drug combinations recited in instant claims 89, 90, 112-119, 133-136, 149, 154, and 156, we conclude that it would have been prima facie obvious to have selected any suitable number of "unique combinations" of "different" compounds to optimize the method for the purpose of systemically and efficiently screening of chemical pools for biological activity. In reaching this conclusion, we find the evidence provided in West, Burgin, and Chiang is sufficient to shift the burden to Appellants to show that the specifically recited numerical combinations would not have been obvious to the skilled worker at the time the invention was made.

The claims also require that "the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells." This limitation would be satisfied if a unique combination contained more than

one active compound. In such a case, the total effect of the combination would be a sum of the effect of each active compound in it. We find this circumstance satisfied in at least the Burgin patent. In Burgin's ribozyme experiments in which a "winning" ribozyme with the highest activity is selected from unique combinations of different ribozyme sequences, it is reasonable to infer that the screened pools may contain more than one active compound. For example, Burgin states that "[i]f one would expect that many combinations within a given pool will be inactive," the number of ribozymes in the pool can be reduced (col. 24, ll. 62-64). In other words, Burgin recognizes that more than one active ribozyme sequence may be present in a single pool.

With respect to claims 91 and 96 which are directed to specific ways of measuring or detecting a biological property of cells, we consider these methods to be conventional as indicated by their description in the application (Specification 7, 21).

With respect to the remaining dependent claims, we find the following disclosure in Stylli to establish their obviousness as conventionally practiced technology in high throughput screening methods:

- Claim 92 (use of a reporter gene in screening libraries at col. 5, ll. 33-58)
- Claim 93 (FRET at col. 28)
- Claim 94 (calcium detection at col. 39, ll. 30-60)
- Claim 95 (fluorescence microscopy at col. 27, ll. 28-45)
- Claims 97, 98, and 155 (any cell line can be used which expresses the desired target at col. 40, ll. 20 to col. 42, l. 9)

- Claims 99, 126, and 142 (the prior art cited in the patent lists "robotics" as useful in automated laboratory testing at p. 2, col. 2)
- Claims 102-106, 108, 110, 120-124, 129, 131, 137-140, 145, 147, 150, and 152 (various chemicals are described, including natural products, small organic molecules, nucleic acids, and peptides; the products can have different levels of purity; at col. 43, ll. 10-45)

*Rejection of claims 100, 101, 127, 128, 143, and 144*

Claims 100, 101, 127, 128, 143, and 144 are rejected under 35 U.S.C. § 103(a) as obvious over Stylli in view of West, Burgin, and Chiang, and further in view of Taylor (U.S. Pat. 6,103,479, issued Aug. 15, 2000; filed May 29, 1997). Taylor teaches that microfluidic devices may be utilized to deliver biologically-active compounds in high throughput screening (Abstract), as recited in claims 100, 127, and 143. Taylor also teaches that ink-jet technology, as recited in claims 101, 128, and 144, is a conventional technology that can be utilized to deliver chemicals (col. 9, ll. 20-21). Thus, the claimed subject matter would have been obvious to the person of skill in the art as the application of a conventionally practiced technology in high throughput screening methods.

*Rejection of claims 107, 109, 111, 125, 130, 132, 141, 146, 148, 151, and 153*

Claims 107, 109, 111, 125, 130, 132, 141, 146, 148, 151, and 153 are rejected under 35 U.S.C. § 103(a) as obvious over Stylli in view of West,

Burgin, and Chiang, and further in view of Cabot (U.S. Pat. 6,982,142 B2, issued Jan. 3, 2006; filed Nov. 30, 1998).

Cabot teaches that drug combinations comprising a chemotherapeutic agent and chemosensitizer can be screened in cell-based assays for synergistic effects (col. 4, ll. 15-27). A chemotherapeutic agent that can be utilized in the screening is tamoxifen (*e.g.*, col. 8, ll. 5-16; cols. 29-30 (Example 7)) which is "an antiestrogen compound used in the treatment of breast cancer." Col. 1, lines 65-66. Because tamoxifen is in clinical use, it is reasonable to presume that it is "an FDA-approved drug" as required by the claims. In sum, it would have been obvious to the person skilled in the art to have included FDA-approved drugs in Stylli's screening method to screen for drug combinations with synergistic effects as taught by Cabot.

TIME PERIOD

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) which provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED; § 41.50(b)

DONALD E. ADAMS )
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